

**REMARKS****I. Detailed Acti n****A. Priority**

The Examiner states that the specification does not comply with one or more conditions for receiving benefit of an earlier filing date under 35 U.S.C. § 120. Applicant has now amended the specification to include the benefit of the continuation of U.S. Patent Application 09/193,653, filed on November 17, 1998. Applicant thanks the Examiner for pointing out this inadvertent mistake.

**B. Election/Restrictions**

The Examiner acknowledges Applicant's election of Group I. Applicant respectfully submits that this election of claims 1-19 was made **with traverse** as indicated in the Response to Restriction Requirement on October 10, 2002. The Examiner further states that claims 20-22 are withdrawn from further consideration as being drawn to a nonelected invention.

**C. Claim Objections**

Claim 12 has been objected to for the abbreviation SRF being used without defining its meaning when initially used. Applicant thanks the Examiner for pointing out the informality. Applicant has amended claim 12 to specifically define the abbreviation SRFs as -- stress response factors --. In light of the above, Applicant respectfully requests that the objection to claim 12 be withdrawn.

**II. Claim Rejections – 35 U.S.C. § 112, Second Paragraph**

Claims 1-19 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Claim 1 stands rejected as vague and indefinite by the phrase "activating and modulating". The Examiner states it is impossible to determine the metes and bounds of the claimed invention.

Applicant respectfully traverses this rejection. Applicant asserts that is essential to understand that "activation and modulation" of macrophages and the immune system are well understood in the art and taught in the specification (see page 3 and page 10). The injection of endotoxin (lipopolysaccharide, LPS) into an animal leads to an immune response that is

heightened to react to an infection but unfortunately kills the host in the process (i.e. toxic shock). The present invention shows that animals fed or injected with a sterile, bacteria-free preparation of stress response factors (SRFs) have a heightened response to infection. Most importantly in the present invention is the fact that the host is not killed. This can also be observed at the cellular level. For example, if monocytes are treated in cell culture with endotoxin, they are "activated" as evidenced by their staying alive for 48 hours and maturing into macrophages. However, the so activated macrophages release a mixture and level of cytokine signals that ultimately cause the death of the host, as observed in animal testing. Exposing the monocytes to SRFs in cell culture also "activates" them to stay alive for 72 hours and to mature into macrophages, but importantly they do not release the level and complex mixture of cytokine signals that leads to the death of the host. Therefore, the monocytes are "activated" to mature into macrophages but are "modulated" not to release those signals or levels that lead to the death of the host when exposure to SRFs occurs. Therefore, Applicant submits that is not unclear what immunological functions the terms encompass nor the metes and bounds of the present invention. Applicant respectfully submits this ground of rejection be alleviated

Claim 1 also stands rejected as vague and indefinite by the phrase "filtering said separated product to remove any stress response products having a molecular weight greater than 10kDa". The Examiner states it is impossible to determine the metes and bounds of the claimed invention.

Applicant respectfully traverses this rejection. However in an effort to expedite prosecution, Applicant has amended the claim to read -- filtering said separated product to remove substances having a molecular weight of greater than 10kDa to form a filtrate --, thus alleviating this rejection. The filtering process not only is removing stress response products but also other substances with a molecular weight greater than 10kDa.

The Examiner rejects claim 8 as vague and indefinite by use of the phrase "37C or less" because there is no lower limit.

Applicant respectfully traverses this rejection. The bacteria were grown in the known and published optimum temperature for growth of that specific organism. However, in order to expedite prosecution, Applicant has amended claim 8 to read -- ranging from approximately 22°C to approximately 37°C --, thereby alleviating this rejection. In addition, claim 9 has been canceled.

Claim 10 stands rejected for the use of the term "stationary phase" as the Examiner states it is unclear whether Applicant is referring to a stage of replication or motility.

Applicant respectfully traverses this rejection. As stated on page 9 of the specification, the stationary phase relates to a particular phase in the life cycle of the bacteria. Particularly, the stationary phase is following the growth phase of the life cycle of all bacteria. The life cycle of bacteria "encompasses a planning phase (lag), a growth phase in which division greatly exceeds death (log), a phase in which growth rates approximate death rates (stationary), and a decline phase in which death greatly exceeds growth (death phase)" (page 11, last paragraph, specification). Applicant asserts the stationary phase has no relation to motility and further that the stationary phase is clearly defined to one skilled in the pertinent art within the specification and is therefore not vague or indefinite. Nonetheless, in an effort to expedite prosecution Applicant has amended the claim to include -- of their life cycle --, to further clarify that the stationary phase is a replication phase within the life cycle of the bacteria, as defined in the specification. In addition, it is well-settled that a patentee is entitled to be his own lexicographer. *See, Digital Biometrics, Inc. v. Identix, Inc.*, 149 F.3d 1335, 1344, 47 U.S.P.Q.2d 1418, 1424 (Fed. Cir. 1998). In view of the foregoing, Applicant respectfully requests that the Examiner's rejection be withdrawn.

The Examiner rejects claim 11 as vague and indefinite by the use of the phrase "molecular weight cutoff of 10,000" as there are no units associated with the number 10,000. Applicant has now amended claim 11 to read -- 10kDa --, thus alleviating this rejection.

Claim 12 stands rejected for insufficient antecedent basis. Applicant thanks the Examiner for pointing out this unintentional error and claim 12 has now been amended to have proper antecedent basis and Applicant has amended claim 1 to include the term stress response factors (SRFs), thereby alleviating this rejection.

The Examiner rejects claim 15 for the use of the phrase "having a size between 0.5 and 3kDa". Applicant has amended claim 15 to now read -- weight -- instead of "size". Applicant respectfully submits this ground of rejection is now alleviated.

Claims 17-19 stand rejected as vague and indefinite for the phrase "sequential periods of stress" as it is unclear what is meant by the phrase.

Applicant respectfully traverses this rejection. The specification clearly states it has "now been found that shorter period of sequential stresses of 20 minutes or less yield more potent SRFs and SRFs of different potencies" (page 12, first and second paragraph, specification). In addition, Applicant asserts that the exact length of time is not as important a factor as being one of a series of washings in aqueous buffers of pH 6.0 to 8.0 (page 12, second full paragraph, specification). Therefore, Applicant asserts that claims 17-19 are not indefinite and would be understood by one skilled in the art to mean "20 minutes or less" as stated in the specification. However, in an effort to expedite prosecution, Applicant has amended claim 17 to include -- of approximately 10-20 minutes -- to further define the periods of stress, thus alleviating this rejection. In addition, Applicant has amended claims 4 and 5 to further define the importance of the aqueous buffers pH values.

In light of the above amendments and remarks, Applicant asserts the claims are now in a condition for allowance. Applicant respectfully requests reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, second paragraph.

### **III. Double Patenting**

Claims 1-19 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 5,840,318.

Applicant is herein submitting a Terminal Disclaimer in compliance with 37 C.F.R. § 1.321(c), which disclaims any term of a patent issuing from this application which would extend beyond the term of U.S. Patent No. 5,840,318 in combination with a Declaration in compliance with 37 C.F.R. § 1.132 stating that any invention disclosed but not claimed in the reference was derived from the inventor of the present application, Dr. William E. Marshall and is thus not an invention "by another" (*see* paragraph 11 of Declaration). Therefore, Applicant submits that the claims are in proper form for allowance and respectfully requests reconsideration and withdrawal of the obviousness-type double patenting rejection.

### **IV. Claim Rejections – 35 U.S.C. § 103(a)**

*35 U.S.C. § 103(a) over U.S. Patent No. 5,840,318:*

Claims 1-19 stand rejected under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 5,840,318. Applicant respectfully submits a Terminal Disclaimer in compliance with 37 C.F.R. § 1.321(c) in combination with a Declaration in compliance with 37 C.F.R. § 1.132

stating that any invention disclosed but not claimed in the reference was derived from the inventor of the present application, Dr. William E. Marshall and is thus not an invention "by another", rendering the rejection to these claims as moot. Applicant respectfully submits that U.S. Patent No. 5,840,318 does not make the claimed invention obvious.

*35 U.S.C. § 103(a) over De Vuyst et al.:*

Claims 1-19 stand rejected under 35 U.S.C. § 103(a) as obvious over De Vuyst et al. Applicant respectfully traverses this rejection. Applicant asserts that the cited reference does not teach, nor does it suggest, the claimed unique invention of the present application. Applicant respectfully requests that this ground of rejection be withdrawn. Submitted herewith for the Examiner's consideration is a § 132 Declaration of the inventor. De Vuyst bacteriocins and Applicant's stress response products is discussed in this § 132 Declaration detailing experiments which distinguish Applicant's SRF's and bacteriocins. Applicant respectfully requests that this declaration be entered and made of record.

Applicant submits that De Vuyst et al. teaches the production of a bacteriocin produced by *Lactobacillus amylovorus* DCE 471 which is bacteriocidal towards closely related *Lactobacillus* strains (page 818). De Vuyst et al. further discloses that the bacteriocin-producing lactic acid bacteria could potentially be added to foods to stimulate bacteriocin production (page 825).

It is submitted that the Examiner is misinterpreting Applicant's invention which is not related to bacteriocins. Submitted herewith is a § 132 Declaration of inventor Dr. Marshall which clearly establishes that the SRF compositions of the invention do not include bacteriocins or other compositions with bactericidal properties. The declaration details several experiments conducted using the standard methods in the art and even used by De Vuyst exposing the test strain for bacteriocins, *Lactobacillus helveticus*, ATCC 15009, to the SRF compositions. The results show that the SRF compositions do not exhibit bactericidal activity. The results as depicted in Figure 1 demonstrate that the preparations of the invention obtained from *L. monocytogenes*, *L. plantarum*, and *E. faecium* do not inhibit growth of *Lactobacillus helveticus*. This is in stark contrast to the bacteriocin Nisin which is shown at the asterisk. Figure 2 shows that stressing *L. monocytogenes*, or even twice stressing *L. plantarum* and *E. faecium* or stressing heat killed *L. plantarum* and *E. faecium* do not result in bacteriocidal activity against *L.*

*helveticus*. Figure 3 demonstrates that bacteriocins against *L. helveticus* are not produced by stressing *L. caseii*, *L. plantarum* or *E. faecium*, again no zones of inhibition are observed from the SRF's. Finally in Figure 4, 7 test strains (5 of *L. plantarum* and 2 of *E. faecium*) were used both as SRF collecting strains and as test strains. Again, the bacteriocin Nisin inhibited all 7 strains while the SRF's collected from the same strains as well as from *L. caseii* did not inhibit growth.

In contrast to the bacteriocin described in De Vuyst et al., the present invention claims the activation and modulation of the immune system of an animal through the administration of a product produced by bacteria subjected to stress which is then filtered. The SRF's stimulate the immune system and it is the host immune system that battles invading bacteria, not other bacteria or bacteriocins. De Vuyst et al. does not disclose the administration of a bacterial product to an animal which has been filtered from the bacteria, and it further does not teach that the product has been filtered to remove any molecules larger than 10 kDa.

*35 U.S.C. § 103(a) over De Vuyst et al., in view of Nanji, or Perdigon or Emery:*

Claims 1-15 and 17-19 stand rejected over De Vuyst et al. in combination with Nanji; which discloses administration of lactic acid bacteria to animals for protection of endotoxin-mediated shock.

Claim 16 stands rejected over De Vuyst et al. in combination with Emery, which teaches the administration of a bacteriocin to create an immunogenic response; or Perdigon, which discloses lactic acid bacteria as adjuvants.

Applicant strongly asserts that neither the suggestion of the claimed unique invention of the present application nor the expectation of success is taught for one ordinarily skilled in the art in the references cited by the Examiner. When prior art references require selective combination to render obvious a subsequent invention, there must be some reason for the combination other than hindsight obtained from the invention itself. It is critical to understand the particular results the new method achieves. See Interconnect Planning Corp. v. Feil, 774 F.2d 1132 (Fed. Cir. 1985). Further, the cited reference does not teach or suggest every element of the claimed invention which must be identically disclosed, in a single reference. See Corning Glass Works v. Sumitomo Electric, 9 U.S.P.Q.2d 1962, 1965 (Fed. Cir. 1989). It is required that "both the suggestion and the expectation of success must be found in the prior art, not in the applicant's

disclosure" and this is not accomplished in regards to De Vuyst et al. See In re Dow Chemical Co., 837 F.2d 469 (Fed. Cir. 1988). Therefore, it is respectfully submitted that any rejection based on the cited references is overly broad because the combination of the references does not render the Applicant's invention, as defined in the claims, obvious. None of the cited references alone or in combination teach, suggest or even mention stress response factors described in Applicant's specification which are distinct, as shown in Applicant's § 132 Declaration, from bacteriocins. In addition, SRFs do not directly kill bacteria as do bacteriocins. Applicant's invention relates to the unique discovery of SRF's which are neither suggested nor taught by De Vuyst.

Nanji teaches a lactobacillus that is acid resistant and able to destroy Gram-negative bacteria. This is a single strain and does not reference applicant's SRF's which are present in all stressed bacteria. In fact Nanji teaches away from the concept that ordinary lactobacilli which do not inhibit *E. coli in vitro* could, when stressed, provide protection against an LPS injection in mice.

Perdigon teaches that the health benefits of feeding milk fermented with lactobacilli is due to an interaction between the bacteria and the milk solids. These effects were limited to and based upon the presence of milk, and again teach away from use of stressed bacteria alone.

The Emery reference teaches bacterial SRP's which are sideophore receptor proteins and are bacterial surface receptors which are similar in acronym only (SRP) to Applicant's factors.

In light of the above remarks and the amended claims, Applicant asserts that the combination of references cited by the Examiner do not teach or suggest the unique method of the present invention and thus would not be obvious to one of ordinary skill in the art. In fact, Applicant respectfully submits that any such suggestion would be merely hindsight application of the Applicant's specification and claimed invention to the cited references. Applicant respectfully requests reconsideration and withdrawal of the rejection to claims 1-19 under 35 U.S.C. § 103(a).

## V. Conclusion

In light of the above amendments and remarks, Applicant asserts that the claims as amended are in a condition for allowance. Applicant respectfully requests reconsideration and withdrawal of the above rejections to claims 1-19.

No fees or extensions of time are believed to be due in connection with this amendment; however, consider this a request for any extension inadvertently omitted, and charge any additional fees to Deposit Account No. 26-0084.

Reconsideration and allowance is respectfully requested.

Respectfully submitted,



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